REMARKS

The specification has been amended to capitalize trademarks and remove reference to embedded hyperlinks.

Applicants have cancelled Claims 9, 10 and 15 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 1-8, 11-12, and 14 to remove reference to the Figures. Claims 1-5 have been amended to add the limitation that the claimed nucleic acids are more highly expressed in normal lung tissue compared to lung tumor, or encode a polypeptide that is more highly expressed in normal lung tissue compared to lung tumor. Claim 14 has been amended to specify the conditions under which hybridization occurs. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments to Claims 1-5 can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification. Support for the amendment to Claim 14 can be found in the definition of stringent conditions in paragraph [0227] of the specification.

Claims 1-8, 11-14, and 16-20 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed September 13, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Specification

URLs:

The Examiner objected to the specification because it contains embedded hyperlinks. Applicants have amended the specification to address the Examiner's concern. In particular, Applicants have replaced the hyperlink with text that describes the location of the website. The amended text no longer constitutes browser executable code.

Continuity:

According to the Office Action, Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(e). Specifically, the Examiner asserts that the applications listed in the first paragraph of the instant specification do not describe or disclose data that would impart specific and substantial utility to the instant invention. Further, the Examiner argues that the instant invention lacks utility. Therefore, the Examiner set as the priority date the filing date of the instant application, May 8, 2002.

Applicants respectfully disagree with the priority date set by the Examiner. In a Preliminary Amendment filed on September 5, 2002, Applicants amended the specification to recite the correct priority for the instant application. The Preliminary Amendment states that the instant "application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/097971 filed 8/26/1998."

The sequences of SEQ ID NOs:87 and 88 were first disclosed in U.S. Provisional Application 60/097971 filed 8/26/1998 in Figures 1 and 2, respectively. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Therefore, the instant application is entitled to an earlier priority date.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-20 as lacking a credible specific and substantial asserted utility, or well-established utility. The PTO states that the specification does not disclose a function for the nucleotide of SEQ ID NO:87 or the polypeptide of SEQ ID NO:88, in the context of the cell or organism. The PTO argues that uses such as hybridization probes, chromosome and gene mapping, the generation of anti-sense RNA or DNA, the preparation of PRO1270 polypeptides and fragments, and generating transgenic or knock-out animals are useful only in

research to determine the function of the encoded protein itself. The PTO asserts that the underexpression of the gene encoding PRO1270 in lung tumors compared to normal lung tissue is not substantial, because a slight increase or decrease in clone copies in tumors is not indicative of a specific or substantial utility for PRO1270 for use as an agent to detect or treat cancer.

Applicants respectfully disagree that they have not established a substantial and specific utility for the claimed invention.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the Gene Encoding the PRO1270 Polypeptide is Differentially Expressed in Lung Cancer compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants submit that the gene expression data provided in Example 18 of the present application, are sufficient to establish a specific and substantial utility for the claimed nucleic acids as diagnostic tools, as described in the specification, for example, at paragraph [0336].

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate

that the genes of interest "can be used to differentiate tumor from normal." He explains that "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). As Mr. Grimaldi states, "If a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor." (Paragraph 7, emphasis added).

The data presented in Example 18 show that the gene encoding PRO1270 is more highly expressed in normal lung tissue compared to lung tumor. As the Grimaldi declaration indicates, the disclosed gene and its corresponding polypeptide and antibodies are therefore useful as diagnostic tools. No additional research into how PRO1270 is related to cancer is required to use the disclosed polynucleotides, polypeptides and antibodies to distinguish tumor cells from their normal tissue counterparts. This establishes a substantial utility for the claimed nucleic acids.

Applicants have Established that the Accepted Understanding in the Art is that there is a Direct Correlation between Comparative mRNA Levels and the Level of Expression of the Encoded Protein in Normal versus Cancerous Tissue

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. In support of their position, Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "[t]hose who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, Dr. Polakis and his colleagues have found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Additional references support this position. For example, Orntoft et al. (submitted herewith as Exhibit 4) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft et al. showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman et al. (submitted herewith as Exhibit 5) showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is

"evidence of a prominent global influence of copy number changes on gene expression levels" (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack et al. (submitted herewith as Exhibit 6) who studied a series of primary human breast tumors and found that "...62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels" (see column 1, abstract). Thus, these articles collectively teach that in general, there is a correlation between gene expression and mRNA expression.

The statements of Grimaldi and Polakis and the references cited above are additionally supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002)). The book teaches the basic principle that there is a correlation between increased gene expression and increased protein expression. It states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA.*" Molecular Biology of the Cell at 302, emphasis added. Similarly, it states while potentially each step on the path from gene to protein can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Molecular Biology of the Cell at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Molecular Biology of the Cell at 379.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of cases, the combined teachings in the art, exemplified by Orntoft et al., Hyman et al., Pollack et al., Molecular Biology of the Cell, and the Grimaldi and Polakis declarations, overwhelmingly teach that gene expression influences mRNA expression and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the gene expression data for the PRO1270 gene, that the PRO1270 protein is concomitantly over-expressed in normal lung cells as compared to lung tumor. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue could be uses as a diagnostic tool, for example, to generate antibodies. It follows that a nucleic acid

which encodes a polypeptide that has use as a diagnostic tool, would likewise have such a use. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would know how to use the PRO1270 polypeptide, and the nucleic acids which encode it, as a cancer diagnostic tool.

Applicants submit that they have therefore established two separate bases for using the claimed nucleic acids. The first argument is based on the differential expression of the PRO1270 gene in normal lung tissue compared to lung tumor. Nucleic acids that can be used to detect the expression of the PRO1270 gene are thus enabled. The second argument is based on the use of the PRO1270 polypeptides as diagnostic tools, given that it is well-established in the art that there is a correlation between gene expression and protein expression. Because it is more likely than not that the PRO1270 polypeptide is differentially expressed in lung cancer, the PRO1270 polypeptides have an enabled use, e.g. generating antibodies. Likewise, nucleic acids encoding these polypeptides also have an enabled use. That includes degenerate nucleic acids as well as homologous nucleic acids which can be used to generate antibodies to PRO1270.

The Claimed Nucleic Acids would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1270, which Applicants submit is not true, a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 4), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 5). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a gene that is differentially expressed in cancer would still have utility as a diagnostic tool. Thus, Applicants have demonstrated another basis of support for the utility of the claimed nucleic acids.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1335 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the disclosed nucleic acids, polypeptides, and antibodies as diagnostic tools.

As discussed above, there are significant data which show that the nucleic acid encoding the PRO1270 polypeptide is more highly expressed in normal lung tissue compared to lung tumor. These data are strong evidence that the gene encoding the PRO1270 polypeptide is associated with lung tumors. Use of the disclosed nucleic acids as diagnostic tools for cancer is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids. Applicants submit that this utility is dependent on the structure of the disclosed nucleic acid molecules and corresponding polypeptides and antibodies, as not all nucleic acids and polypeptides which are present in lung tumors are underexpressed compared to their normal tissue counterparts. Thus, contrary to the assertions of the PTO, Applicants submit that they have established that the asserted utilities are specific to the claimed nucleic acids.

Conclusion

The PTO has asserted that the claimed invention lacks a substantial and specific utility. Applicants submit that they have established that the claimed nucleic acids have both a substantial and a specific utility.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1270 gene in normal lung tissue compared to lung tumor are real and significant. This declaration also indicates that given the relative difference in expression levels, the claimed nucleic acids have utility as cancer diagnostic tools.

Next, Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the PRO1270 protein and antibodies have utility as diagnostic tools for cancer, further supporting the asserted utility of the claimed nucleic acids.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, a gene differentially expressed in cancer is useful as a diagnostic tool.

Finally, Applicants have pointed out that the substantial utilities described above are specific to the disclosed nucleic acids because the gene encoding PRO1270 is differentially expressed in certain cancer cells compared to the corresponding normal cells. The utility of a diagnostic tool for cancer is not a general utility that would apply to the broad class of nucleic acids.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the asserted utility for the disclosed nucleic acids, polypeptides, and antibodies relating to PRO1270. In view of the above, Applicants respectfully request that the PTO withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. §112, first paragraph – Enablement

The Examiner rejected Claims 1-20 under 35 U.S.C. § 112, first paragraph. According to the Examiner, because the claimed invention is not supported by either a substantial asserted utility or a well established utility, on of skill in the art would not know how to use the invention. The Examiner also argues that the specification does not reasonably provide enablement for all variants of the PRO1270 polypeptide.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Specifically, the claimed polypeptides have utility in the diagnosis of lung cancer. Also, as set forth above, Claims 1-5 have been amended to recite the functional limitation "wherein said isolated polypeptide is more highly expressed in normal lung tissue compared to lung tumor, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal lung tissue compared to lung tumor." Thus, the specification teaches how to make and use the claimed subject matter. Specifically, the specification describes how to make the claimed polypeptides and how to assay for the claimed function in the variant polypeptides. Based upon that teaching and the above-established utility for the claimed subject matter, one skilled in the art would know how to make and use the claimed subject matter.

Further, the PTO asserts that the results of the experimental assays are not substantial because "it is known in the art that increased mRNA levels do not necessarily correlate to an increase in protein production, or do not correlate well." The Examiner relies upon Haynes *et al.* (1998, *Electrophoresis*, 19:1862-1871), asserting that Haynes found that for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Haynes supported the Examiner's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Haynes does not contradict the utility or enablement of the instant claims. Specifically, Haynes does not address the issue of whether levels of mRNA in a tumor cell compared to a normal cell typically correlate to a similar increase/decrease in the amount of the encoded protein

in the tumor cell relative to the normal cell. For example in the case of increased expression of a particular mRNA in a lung tumor cell compared to a non-cancerous lung cell, Haynes does not address whether one would expect to see a corresponding increase in expression of the particular encoded protein in the lung tumor cell compared to the normal lung cell.

Haynes is 1998 a review article dealing with the art of proteome analysis. Haynes studied 80 selected samples, all from one organism, *Saccharomyces cerevisiae*. Haynes considered whether different genes with roughly equivalent mRNA levels would correspond to equivalent protein levels for the different genes. Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." Thus, it is not even clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, with some exceptions. For some of the studied genes, Haynes reported differences in protein expression between different genes, including some that varied by more than 50-fold. Thus, Haynes showed that for one type of yeast organism, *Saccharomyces cerevisiae*, similar mRNA levels for different genes did not universally result in equivalent protein levels for the different genes. This is different from whether increased mRNA levels for a single gene in one cell type compared to the same gene in a different cell type, would also correspond to increased protein levels in the one cell type compared to the different cell type. Therefore, Haynes is not inconsistent with or contradictory to the utility or enablement of the instant claims.

Applicants submit that undue experimentation would not be required to use the claimed nucleic acids as diagnostic tools. The level of skill in the art is high, and methods of using nucleic acid sequences as probes are well-known and well-established in the art. One of skill in the art would know how to use the claimed nucleic acids, for example, as hybridization probes for the diagnosis of cancer as outlined in the specification at, for example, paragraph [0336], and Example 18 beginning at paragraph [0529].

Applicants therefore request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §112, first paragraph – Written Description

The Examiner asserts that Claims 1-6, 8-10 and 14-20 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner notes that the claims are directed to nucleotides that

encode a polypeptide having the sequence of SEQ ID NO:88, variant polypeptides that are 80%-99% identical to SEQ ID NO:88 or various portions thereof. However, the Examiner argues that such claims are not described because the specification does not teach functional or structural characteristics of all of the claimed polynucleotides.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The subject matter of the pending claims concerns nucleic acids having a specified sequence identity with the disclosed polynucleotide sequence of SEQ ID NO:87, or encoding a polypeptide with the specified polypeptide sequence of SEQ ID NO:88, and as amended, with the functional recitation: "wherein said isolated nucleic acid is more highly expressed in normal lung tissue compared to lung tumor, or wherein said isolated nucleic acid

encodes a polypeptide that is more highly expressed in normal lung tissue compared to lung tumor." Other claims relate to nucleic acids which hybridize to nucleic acids of SEQ ID NO:87, or polynucleotides which encode a polypeptide of SEQ ID NO:88, under the specified stringent conditions.

Based on the detailed description of the cloning and expression of variants of PRO1270 in the specification, the description of the gene expression assay, the actual reduction to practice of sequences SEQ ID NOs:87 and 88, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the subject matter of the pending claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-20 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the recitation of "the extracellular domain," since an extracellular domain is not recognized in secreted proteins. Applicants have amended the claims to remove any reference to an extracellular domain.

The PTO has also rejected Claim 15 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the use of "stringent conditions." Claim 15 has been canceled. Applicants have amended Claim 14 to specify the stringent conditions under which hybridization is assessed.

In light of the above, Applicants request that the PTO withdraw the indefiniteness rejections under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(a) – Anticipation

The PTO rejects Claims 1-5 and 16-19 as anticipated under 35 U.S.C. § 102(a) by Suzuki et al. (Accession No. AF271386, 2002). The PTO asserts that Suzuki et al. disclose a polynucleotide sequence which is 99% similar to PRO1270.

The PTO also rejects claims 1-5 and 16-19 as anticipated under 35 U.S.C. § 102(b) by Tsuji et al. (2001 J. Biol. Chem., 276(26):23456-23463). The PTO asserts that this reference teaches a nucleic acid sequence that is 99% similar to PRO1270.

Applicants respectfully traverse.

As noted above, the data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polynucleotides, were

first disclosed in PCT Application PCT/US00/23328 filed August 24, 2000, on page 93, line 3, through page 96, line 35. Applicants are fully entitled to the benefit of this earlier filed application. As such, neither the 2002 Suzuki reference or the 2001 J. Biol. Chem. Reference is available as prior art under §102. Applicants therefore respectfully request that the rejection under 35 USC §102 be withdrawn.

Rejection under 35 U.S.C. §103(a) – Obviousness

Claim 20 is rejected under 35 U.S.C. § 103(a) by Tsuji et al. (2001 J. Biol. Chem., 276(26):23456-23463) in view of Gray et al. (1992, U.S. Patent No. 5,169,762). Gray et al discuss expression of nucleic acid in a variety of prokaryotic and eukaryotic cells. Thus, according to the Examiner, it would have been obvious to use a variety of art recognized vectors to express the polypeptide of SEQ ID NO:88.

As noted above, Applicants are fully entitled to the benefit of PCT Application PCT/US00/23328 filed August 24, 2000. As such, the 2001 J. Biol. Chem. Reference is not available as prior art under §103. Applicants therefore respectfully request that the rejection under 35 USC §103 be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Dec. 7, 2004

By: AnneMarie Kaiser

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